REMARKS

In the Final Action dated July 26, 2005, claims 1-18 and 79-137 are pending, of which claims 4-8, 17, 79-80, 89-99, 101, 107, 111-115 and 121-123 are withdrawn from consideration. Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, and 124-125 are under examination and are rejected.

This Response addresses each of the Examiner's rejections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

The Examiner has objected to the term "derivative or equivalent" of GPI recited in the claims. The Examiner acknowledges that the specification discloses that GPIs consist of a conserved core glycan, Manα1-2Manα1-6Manα1-4GlcNH$_2$, linked to the 6 position of the myo-inositol ring of PI. However, the Examiner indicates that the specification also discloses other GPIs that do not appear to contain the conserved core glycan, for example, EtN-P-Manα2-Manα6-M-Y (page 4 at line 2) and Manα2-Manα6-M-Y (page 7 at line 1). The Examiner contends that the genus of GPI molecules cannot be defined merely by a function (i.e., activating helper T cells via an interaction with CD1), as presently claimed.

In response, Applicants have amended the independent claims to delete the reference to "derivative or equivalent" of GPI, and to define the structure of the GPI molecule by its conserved core glycan. Applicants have also amended the dependent claims to delete those formulas that do not contain the conserved core glycan. Applicants respectfully submit that the genus of GPI molecules encompassed by the present claims, are now characterized both by a characteristic structural feature,

i.e., comprising the recited core glycan, as well as a functional feature, i.e., activating helper T cells via an interaction and association with CD1. According to the Guidelines for the Examination of Patent Application under the 35 U.S.C. 112, first Paragraph, "Written Description Requirement", 66 Federal Register 1099-1111 (2001), possession of the invention can be shown by either actual reduction to practice, or by describing the invention with sufficiently detailed, relevant identifying characteristics, such as complete or partial structure, physical and/or chemical properties, correlation between structure and function, or some combination thereof. *Id.*, at 1106.

Applicants respectfully submit that the genus of GPI molecules, as presently claimed, is adequately described both structurally and functionally, in full compliance with the written description requirement. Withdrawal of the written description rejection under 35 U.S.C 112, first paragraph, is therefore respectfully requested.

Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 are rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement. The Examiner alleges that the specification does not provide sufficient teaching on how to practice the claimed method of activating T helper cells by administering a T cell activating amount of GPIs, or the claimed method of inducing in a mammal an immune response directed to GPI.

It is observed that the first aspect of the rejection is directed to the recitation of "derivative or equivalent" of GPI molecules. In view of the cancellation of the reference to "derivative or equivalent" of GPI molecules, this aspect of the rejection is rendered moot.

It is further observed that the second aspect of the rejection is directed to treatment or prophylaxis of a condition or disease in a mammal. The Examiner states that the specification does not provide any working examples of treatment of prophylaxis of any condition *in vivo*, including in a mammal by administering a GPI molecule. The Examiner has referenced the Schofield et al. article (*Nature* 418:785-789, 2002), which discloses activation of Th cells to induce an antibody response in

mice infected with *P. berghei*. However, the Examiner argues that the claims are not limited to induction of an antibody response in infected mice, but are directed to treatment or prophylaxis of *any* disease condition, in *any* mammal. In addition, the Examiner has referenced passages in the Schofield et al. article, where the authors state that it is yet to be determined as to whether GPI is a target of clinical immunity, and that the *P. berghei*-infected mouse model may not adequately reflect the aspects of human malaria anemia.

Applicants believe that this second aspect of the enablement rejection should apply, if at all, only to claims 103, 109, 124 and their dependent claims, which are directed to methods for the treatment and/or prophylaxis of a mammalian disease condition by administering to the mammal an effective amount of GPI or a complex comprising said GPI.

Furthermore, Applicants respectfully submit that the Examiner's interpretation and assessment of the relevance of the Schofield (2002) article is incorrect. Applicants respectfully submit that the article disclosed the finding that, in the context of eliciting an antibody response against GPI, it is necessary that the GPI molecule be administered without a lipid component. The inclusion of a lipid component in fact resulted in an adverse response. Specifically, the authors made the observation that mice immunized with purified, intact, free GPI, mounted an IgM-dominated response directed predominantly to the lipidic domain of the molecule, wherein the antibodies cross-reacted with host GPI lipidic domains that were exposed at host cell surfaces. This resulted in the induction of a cross-reactive immune response against non-foreign antigens, specifically GPI-anchored self molecules. The antibodies that are generated in this type of response were not clinically protective against subsequent parasite infection and, in fact, passive transfer of these antibodies exacerbated disease severity. However, immunization with the delipidated glycan domain of malarial GPI resulted in IgG antibodies interactive with the glycan domain of GPI, and animals thus immunized were substantially protected against pathology induced by subsequent malaria challenge. Passive transfer of these IgG antibodies

was protective against pathology. The authors therefore demonstrated that IgM antibodies to the lipidic domain and IgG antibodies to the glycan domain of the malaria GPI differ in their effects, the former promoting disease and the latter preventing it.

The present invention, however, relates to the induction of a CD1-mediated helper T cell response through CD1-restricted recognition of the GPI moiety. In order to achieve this CD1-restricted recognition, however, it is essential that the GPI molecule is lipidated. This is in complete contrast to the nature of the molecule discussed in Schofield et al. (2002). In the absence of lipidation, there cannot be achieved a CD1 restricted T helper cell response.

Moreover, with respect to the passages in the Schofield et al. (2002) article regarding potential limitations of the *P. berghei*-infected mouse model, Applicants respectfully submit that the authors merely noted certain adverse responses that were observed in the mice, for example, the occurrence of hemolytic anaemia. Applicants respectfully submit that these are not responses that occur in humans and are therefore irrelevant to clinical applications to humans.

Applicants respectfully submit that the present specification provides sufficient guidance for those skilled in the art to practice the methods as presently claimed without undue experimentation. As such, Applicants respectfully submit that the enablement rejection under 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is respectfully requested.

Claims 1-3, 9-18, 81-88, 100, 102-106, 108, 109, 116-120, 124 and 125 are rejected under 35 U.S.C. §102(b), as anticipated by Schofield et al. (*J. Exp. Med.* 177:145-153, 1993), as evidenced by Nagata et al. (*Eur. J. Immunol.* 1993 23:1193-1196).

The Examiner contends that Schofield et al. (1993) teach administration of GPI, which would inherently result in GPI binding to CD1 and activation of Th cells, and therefore meet the limitations of the claims.

Applicants respectfully submit that Schofield et al. (1993) merely describe GPI as a toxin and observe that a seralogical response can be induced by GPI, which response exhibits T cell-independent features. It is important to recognize that GPIs are a complex class of molecules, with one GPI varying from another GPI on the basis of the extent and complexity of the molecular branches which are linked to a core glycan. The presently claimed methods are directed to administration of GPI characterized by a specified core glycan and capable of activating T cells via interaction with CD1. Schofield et al. (1993) do not teach anywhere the structure of GPI molecules that is required to induce a CD1 restricted response. Accordingly, Applicants respectfully submit that the reference does not teach the methods as presently claimed.

Furthermore, Applicants respectfully submit that the rejection is improper insofar as claims 103-106, 108-109, 116-120 and 124-125 are concerned. These claims are directed to methods of treatment and/or prophylaxis of a disease or condition by administration of GPI. Schofield et al. (1993) merely teach that administration of GPI to mice induced a serological response with T-independent features. The reference does not teach administration of GPI for the purpose of treatment and/or prophylaxis of a disease or condition, or at least there is no demonstration or showing that administration of GPI to a mammal actually treated or reduced the risk of a disease or condition in the mammal. To highlight the distinction of the claimed invention from the Schofield et al. (1993) reference, Applicants have amended independent claims 103, 109 and 124 to add at the end of the claims: "thereby treating said condition or reducing the risk of developing said condition." Support for this language is found in the specification, e.g., the paragraph bridging pages 44-45.

In view of the foregoing, it is respectfully submitted that the §102(b) rejection based on Schofield et al. (1993) is overcome. Withdrawal of the rejection is respectfully requested.

Claims 11-13, 86-88 and 116-118 are rejected under 35 U.S.C. §102(a) as anticipated by Schofield et al. (*Science* 283:225-229, January 1999), as evidenced by van Joost et al. (*J. Amer. Acad.*

Dermatol. 27:922-8, 1992) and Paul (*Fundamental Immunol.* 2nd Ed., 1989, New York, Raven Press, page 405).

It is the Examiner's position that the foreign priority document, AU PP 6758, does not disclose the chemical species recited in the rejected claims. Further, it is the Examiner's position that a disclosure of the genus of "GPI" does not provide support for the subgenus and species recited in the rejected claims.

Applicants intend to submit a Katz Declaration to overcome the instant rejection.

Claims 11, 13, 86, 88, 116 and 118 are rejected under 35 U.S.C. §102(a) as anticipated by WO 99/52547 (10/21/99). Specifically, the Examiner contends that the GPI species recited in the rejected claims are not entitled to the priority date of AU PP 6758, and are therefore anticipated by WO 99/52547.

Applicants respectfully submit that the Examiner's rejection is improper. Even assuming, *pro arguendo*, that the GPI species recited in the rejected claims are not entitled to the priority date of AU PP 6758, these GPI species are not disclosed in WO 99/52547 in any event. It is improper for the Examiner to allege deficiencies of the instant priority document on one hand, and to rely on a generic disclosure of the reference to reject the claims on the other hand. Thus, Applicants respectfully submit that WO 99/52547 does not provide adequate teaching to anticipate the subject matter of Claims 11, 13, 86, 88, 116 or118. Withdrawal of the rejection is respectfully requested.

Claims 11-13, 86-88, 116-118 are rejected under 35 U.S.C. §103(a) as obvious over WO 99/52547 (10/21/99), in view of Tachado et al. (*PNAS USA* 94: 4022-4027, 1997) and Joyce et al. (*Science* 279: 1541-1543, 3/6/98).

The Examiner admits that WO 99/52547 does not teach the treatment of malaria or other parasitic infections by administering a GPI that comprises diacylglycerol. The Examiner contends that such teaching is supplied by the secondary references.

Applicants respectfully submit that as asserted above, WO 99/52547 is not a proper prior art in the first instance with respect to the GPI species specifically recited in the rejected claims. This fundamental deficiency of WO 99/52547 is not cured by the secondary references, taken alone or in combination. Thus, the §103(a) rejection is overcome and withdrawal thereof is respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

Frank S. DiGiglio
Registration No. 31,346

Scully, Scott, Murphy & Presser
400 Garden City Plaza, Suite 300
Garden City, New York 11530
(516) 742-4343
FSD/XZ:bk